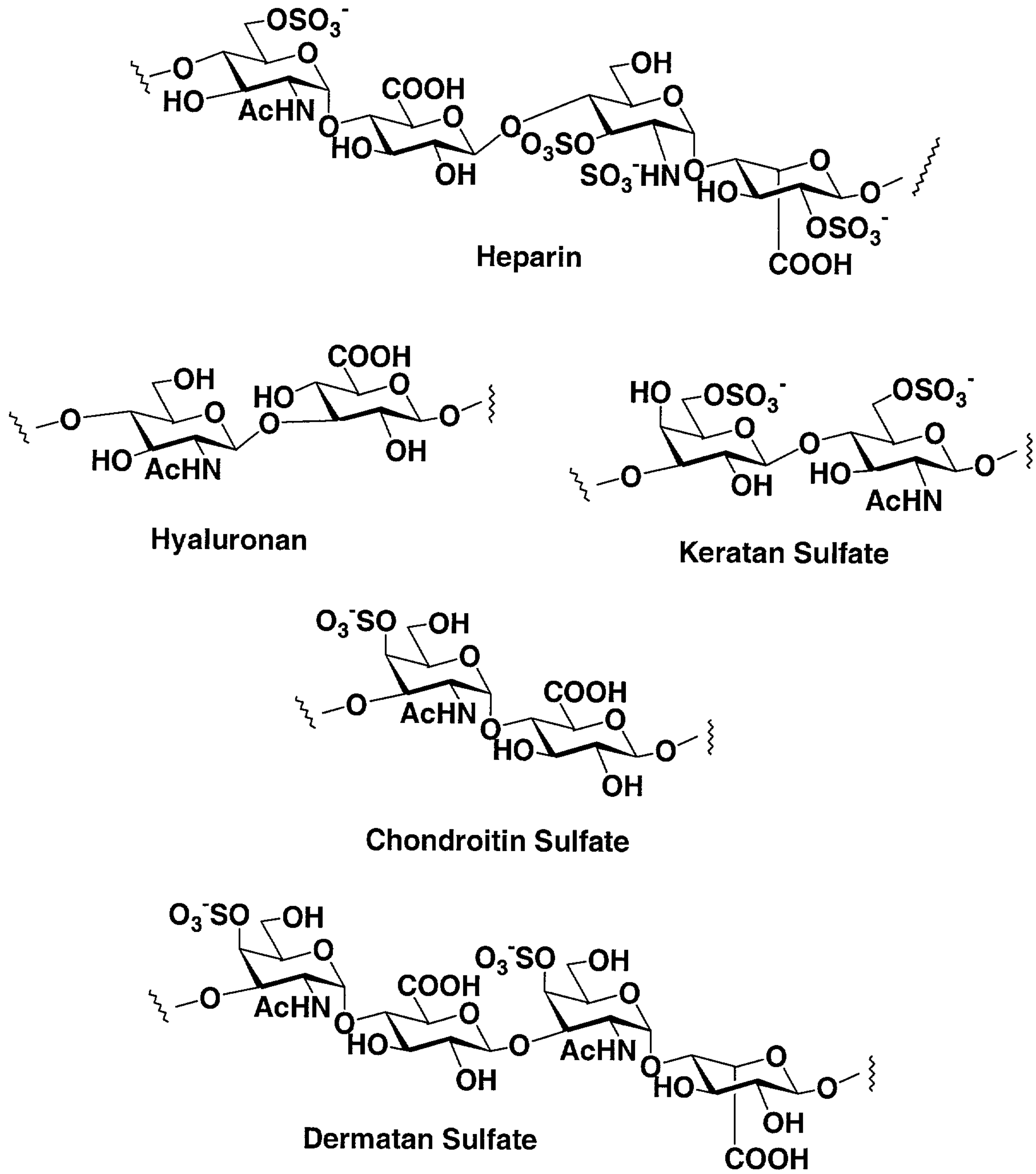
Figure 1



Heparin
Hyaluronan
Keratan Sulfate
Chondroitin Sulfate
Dermatan Sulfate

Figure 2

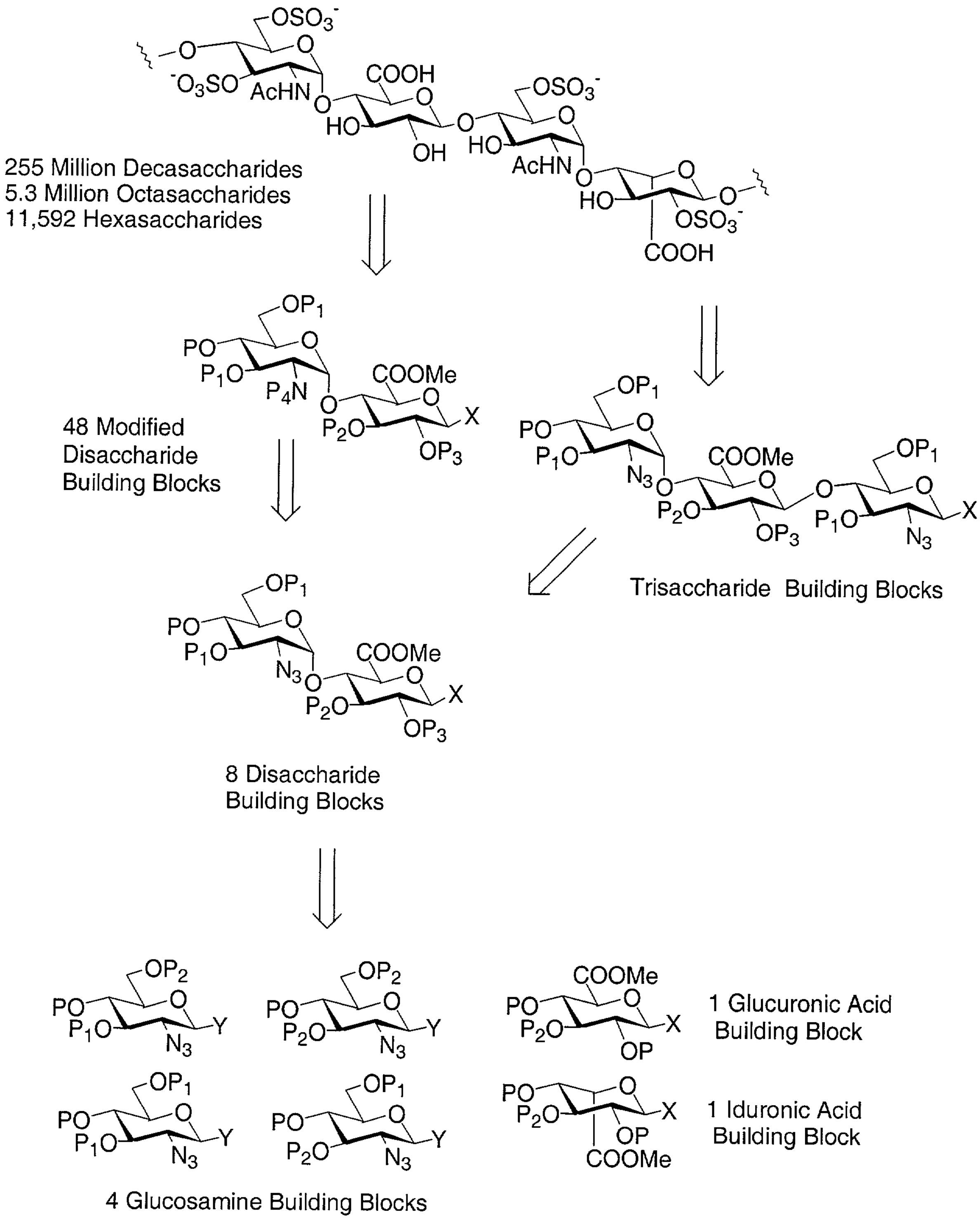
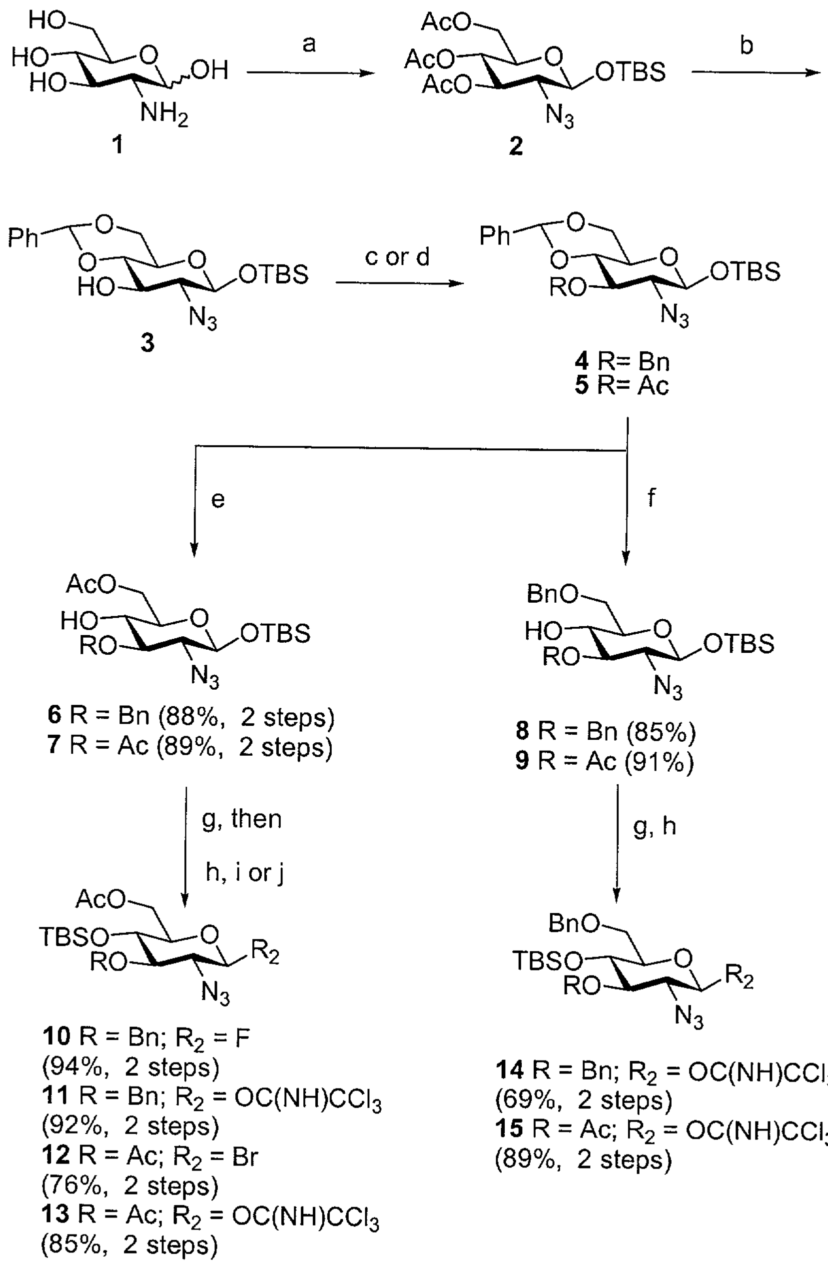
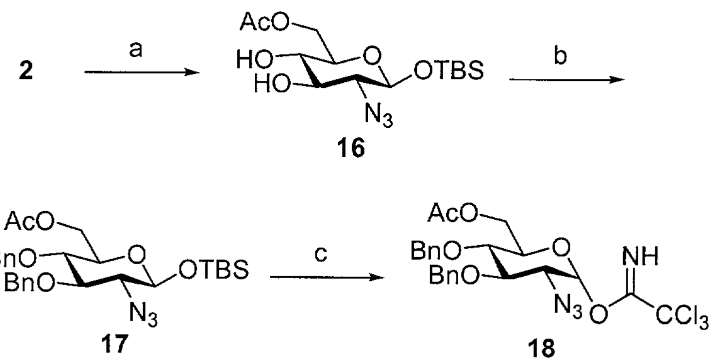

255 Million Decasaccharides
5.3 Million Octasaccharides
11,592 Hexasaccharides
48 Modified
Disaccharide
Building Blocks
Trisaccharide Building Blocks
8 Disaccharide
Building Blocks
4 Glucosamine Building Blocks
1 Glucuronic Acid
Building Block
1 Iduronic Acid
Building Block

Figure 3



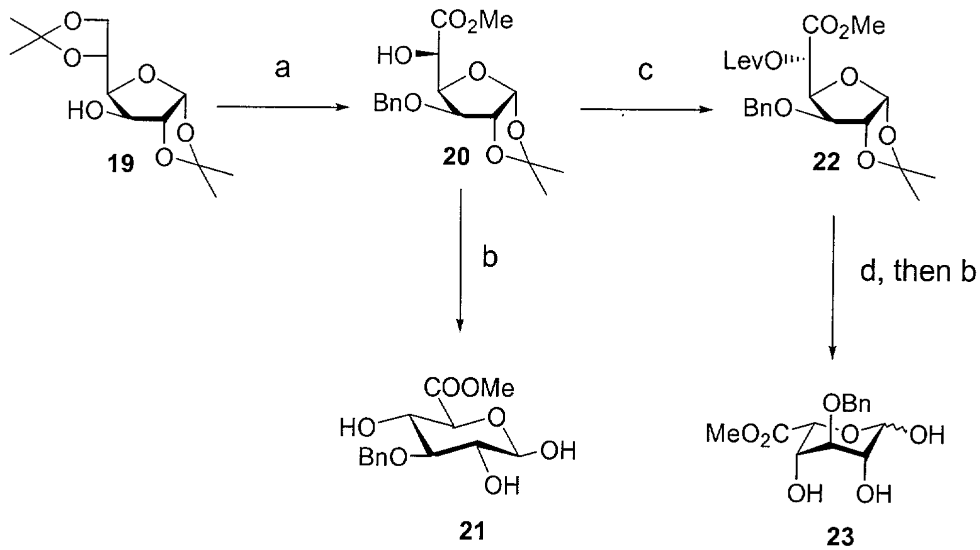
a) 1. TfN_3, H_2O, K_2CO_3, CH_2Cl_2, MeOH, $CuSO_4$; 2. Ac_2O, pyridine, DMAP; 3. NH_3, MeOH, THF; 4. TBSCl, imidazole, CH_2Cl_2, 72% (four steps);
b) 1. NaOMe, MeOH; 2. $PhCH(OMe)_2$, pTsOH, CH_3CN, 86% (two steps);
c) BnBr, Ag_2O, 4Å molecular sieves, CH_2Cl_2, 95%; d) Ac_2O, DMAP, pyridine;
e) 1. TFA (60% aq.), CH_2Cl_2; 2. AcCl, collidine, -40°C; f) TES, TFA, CH_2Cl_2;
g) 1. TBSOTf, lutidine, CH_2Cl_2; 2. TBAF, AcOH, THF; h) CCl_3CN, DBU, CH_2Cl_2;
i) DAST, CH_2Cl_2, 0°C; j) $SOBr_2$, imidazole, THF.

Figure 4



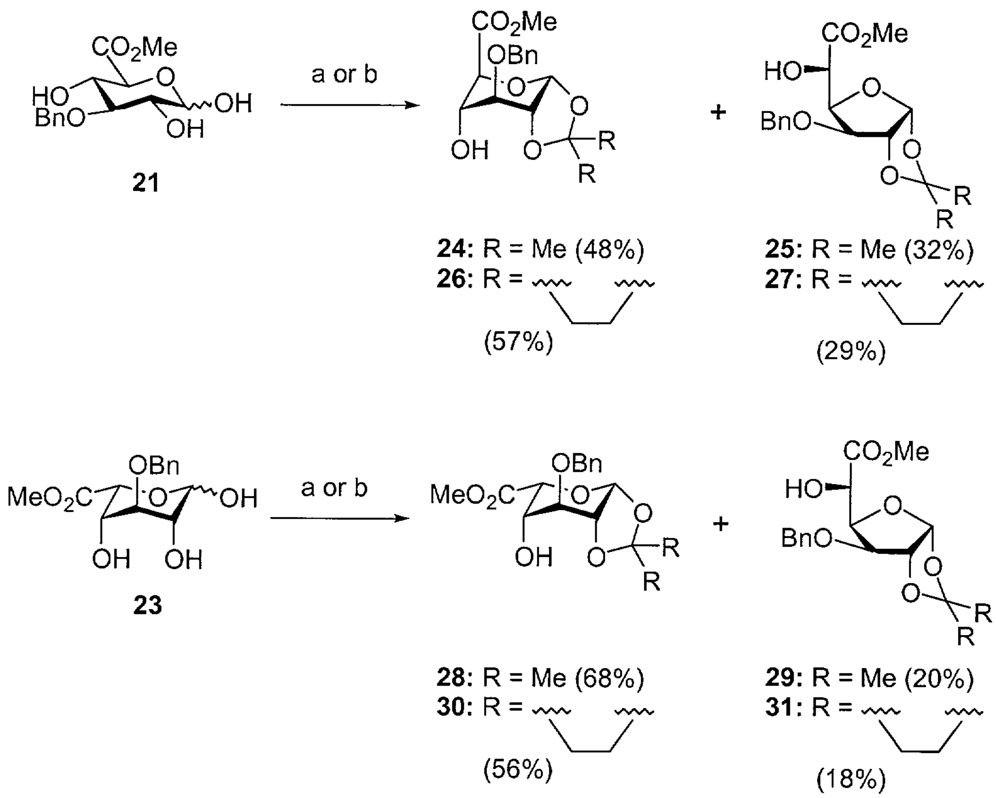
a) 1. NaOMe, MeOH; 2. AcCl, collidine, -40°C, 93% (two steps);
b) BnBr, Ag_2O, 4Å molecular sieves, CH_2Cl_2, 80%;
c) 1. THF, AcOH, TBAF; 2. CCl_3CN, DBU, CH_2Cl_2, 88% (2 steps).

Figure 5



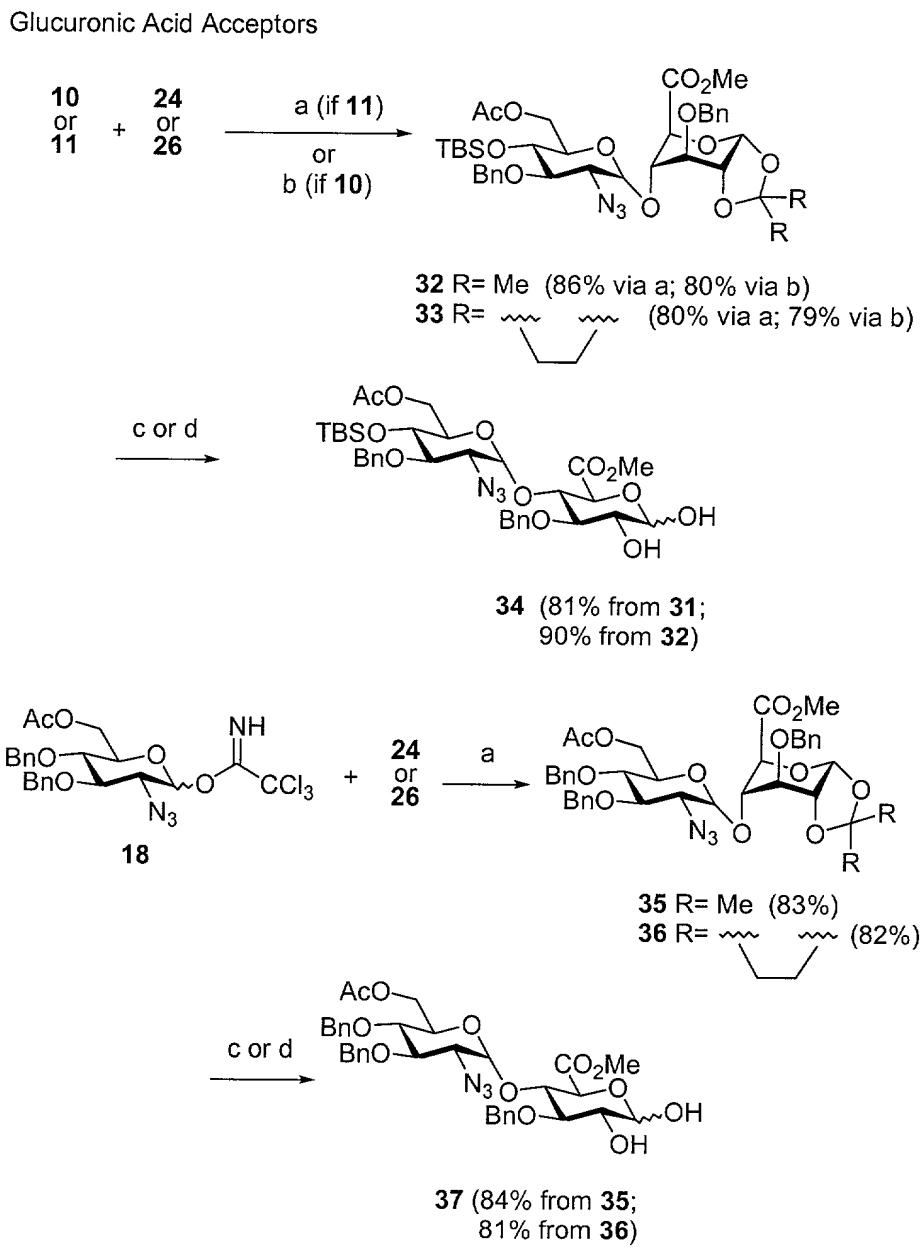
a) 1. NaH, BnBr, THF, Bu_4NI; 2. aq. HOAc (66%), 40°C; 3. TBSCl, DMAP, CH_2Cl_2, pyridine; 4. Ac_2O, DMAP, pyridine; 5. HF-pyridine, THF; 6. TEMPO (cat.), KBr, Bu_4NBr, $NaHCO_3$, NaOCl, CH_2Cl_2/H_2O; 7. 4M NaOH, MeOH; 8. MeI, $KHCO_3$, DMF, 65% (eight steps); b) TFA (90% aq.), quant; c) 1. Tf_2O, pyridine, CH_2Cl_2; 2. LevONa, DMF, 80°C, 82% (two steps); d) N_2H_4, HOAc, pyridine, 91%.

Figure 6



a) 2-methoxypropene, DMF, CSA;
b) methoxycyclopentene, DMF, CSA.

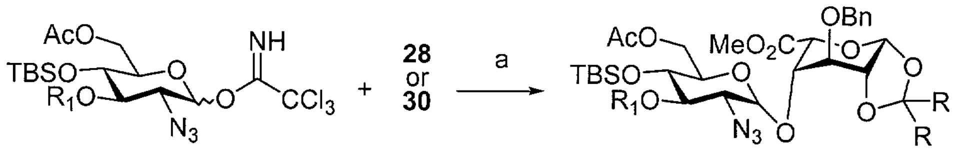
Figure 7



a) TBSOTf, 4Å molecular sieves, CH_2Cl_2, -78°C to rt;
b) $AgClO_4$, $SnCl_2$, Et_2O, 4Å molecular sieves, 0°C to rt;
c) dichloroacetic acid (75% aq.);
d) dichloroacetic acid (50% aq.);
e) dichloroacetic acid (60% aq.)

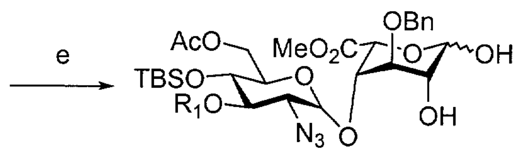
Figure 8

Iduronic Acid Acceptors



11 R_1 = Bn
13 R_1 = Ac

39 R_1 = Bn; R= Me (91%)
40 R_1 = Ac; R= Me (90%)
41 R_1 = Ac; R=  (88%)

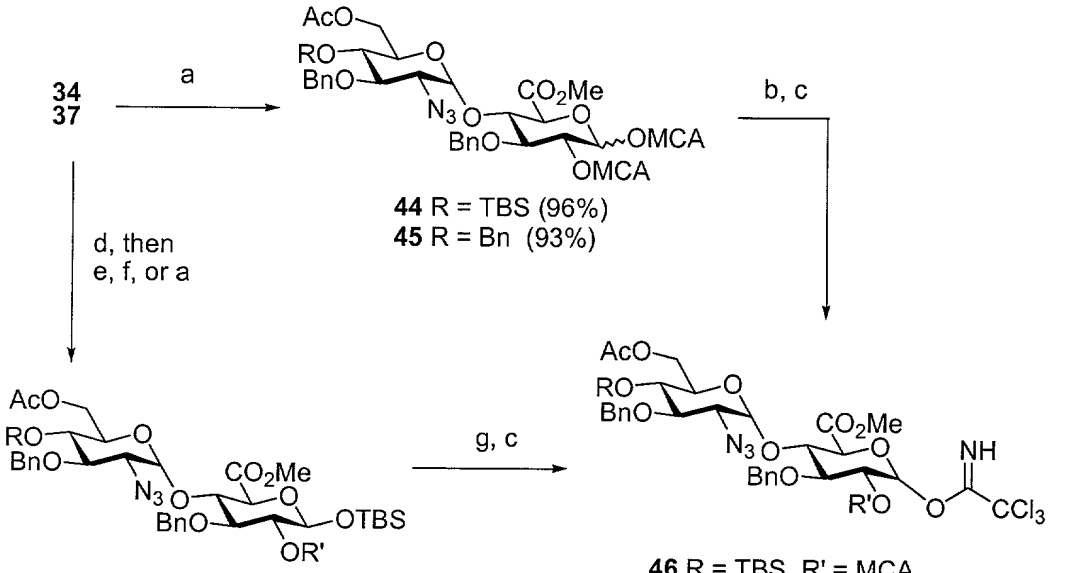


42 R_1 = Bn (92%)
43 R_1 = Ac (89% from **30**)
(88% from **31**)

a) TBSOTf, 4Å molecular sieves, CH_2Cl_2, -78°C to rt;
b) $AgClO_4$, $SnCl_2$, Et_2O, 4Å molecular sieves, 0°C to rt;
c) dichloroacetic acid (75% aq.);
d) dichloroacetic acid (50% aq.);
e) dichloroacetic acid (60% aq.)

Figure 9

Glucuronic Acid Disaccharide Donors

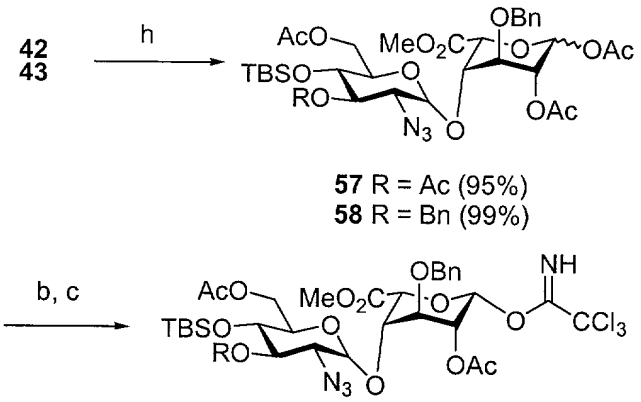


44 R = TBS (96%)
45 R = Bn (93%)

48 R = TBS, R' = Lev (81%)
49 R = TBS, R' = Alloc (76%)
50 R = TBS, R' = MCA (82%)
51 R = Bn, R' = Lev (80%)
52 R = Bn, R' = Alloc (73%)

46 R = TBS, R' = MCA
(64% from **44**; 36% from **50**)
47 R = Bn, R' = MCA (68% from **45**)
53 R = TBS, R' = Lev (92%)
54 R = TBS, R' = Alloc (68%)
55 R = Bn, R' = Lev (85%)
56 R = Bn, R' = Alloc (83%)

Iduronic Acid Disaccharide Donors

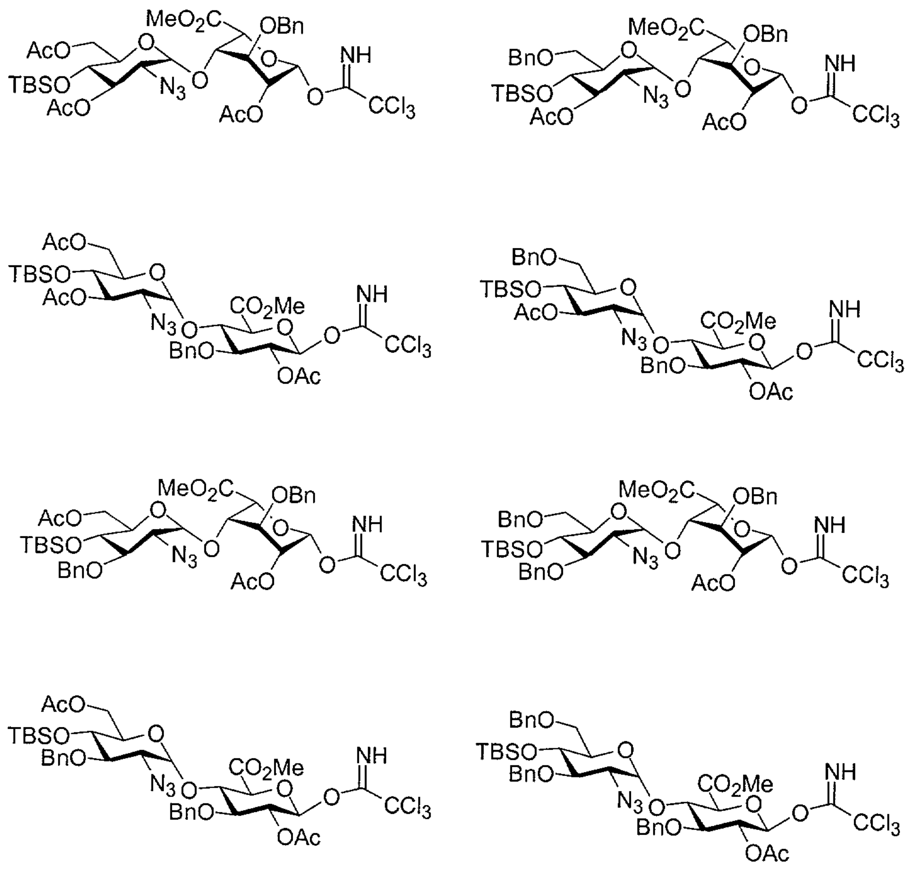


57 R = Ac (95%)
58 R = Bn (99%)

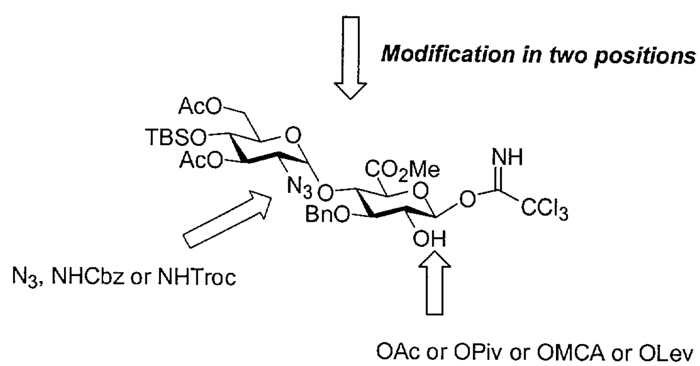
59 R = Ac (67%)
60 R = Bn (75%)

a) $(MCA)_2O$, CH_2Cl_2, DMAP, pyridine; b) $BnNH_2$, ether, 0°C;
c) $NCCCl_3$, DBU, CH_2Cl_2; d) TBSCl, imidazole, CH_2Cl_2;
e) $(Lev)_2O$, DMAP, CH_2Cl_2; f) AllocCl, DMAP, CH_2Cl_2;
g) TBAF, HOAc, THF; h) Ac_2O, CH_2Cl_2, DMAP, pyridine.

Figure 10

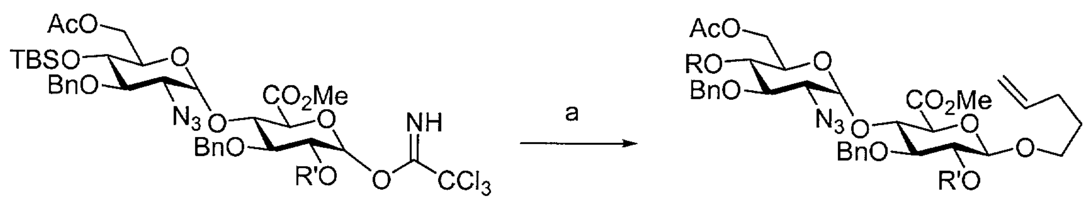


8 Disaccharide Modules



48 Disaccharide Modules

Figure 11

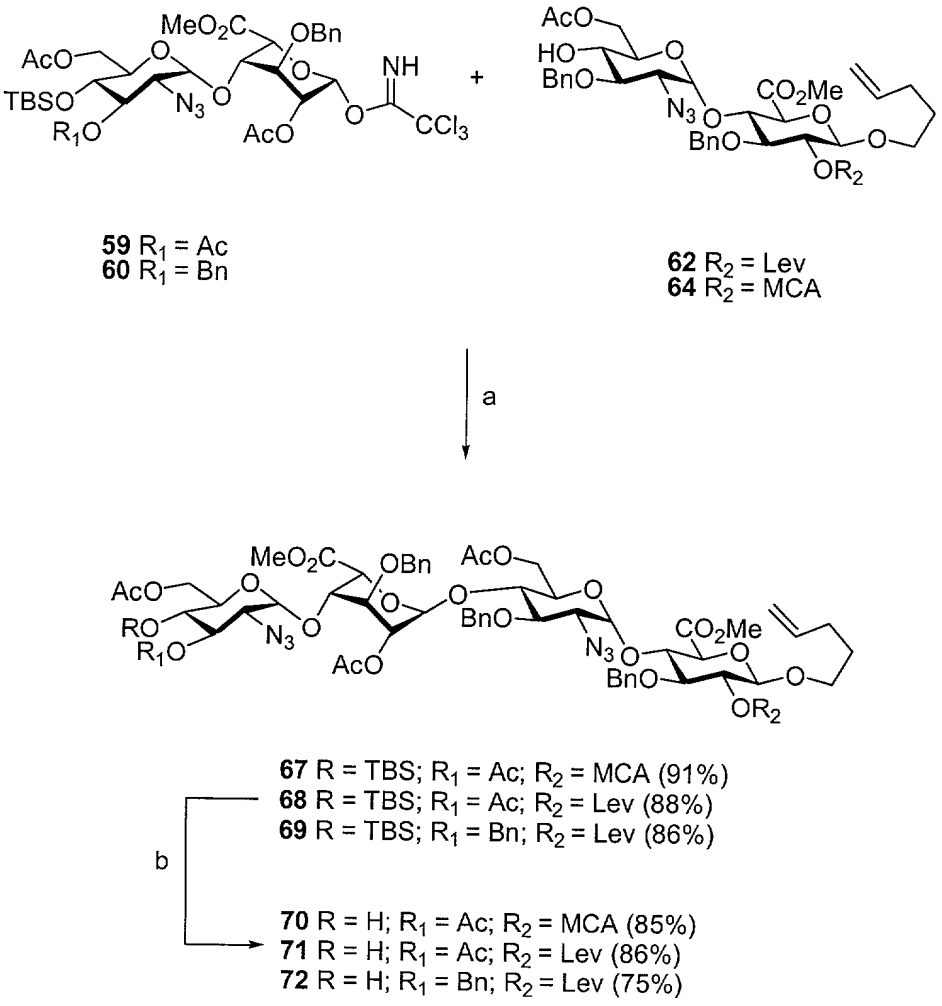


53 R' = Lev
46 R' = MCA
54 R' = Alloc

b: **61** R = TBS, R' = Lev (75%) → **62** R = H, R' = Lev (85%)
b: **63** R = TBS, R' = MCA (70%) → **64** R = H, R' = MCA (85%)
b: **65** R = TBS, R' = Alloc (66%) → **66** R = H, R' = Alloc (85%)

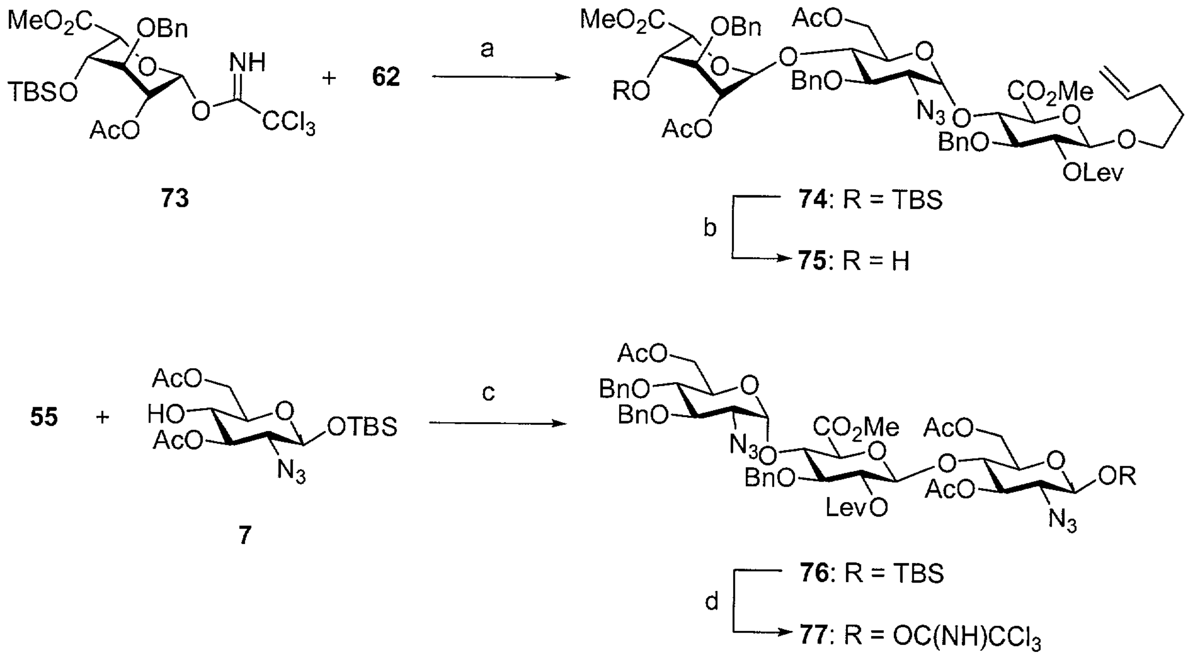
a) 4-penten-1-ol, TMSOTf, CH_2Cl_2, 0°C;
b) HF-pyridine, HOAc, THF.

Figure 12



a) TMSOTf, CH_2Cl_2, -20°C; b) HF-pyridine, AcOH, THF.

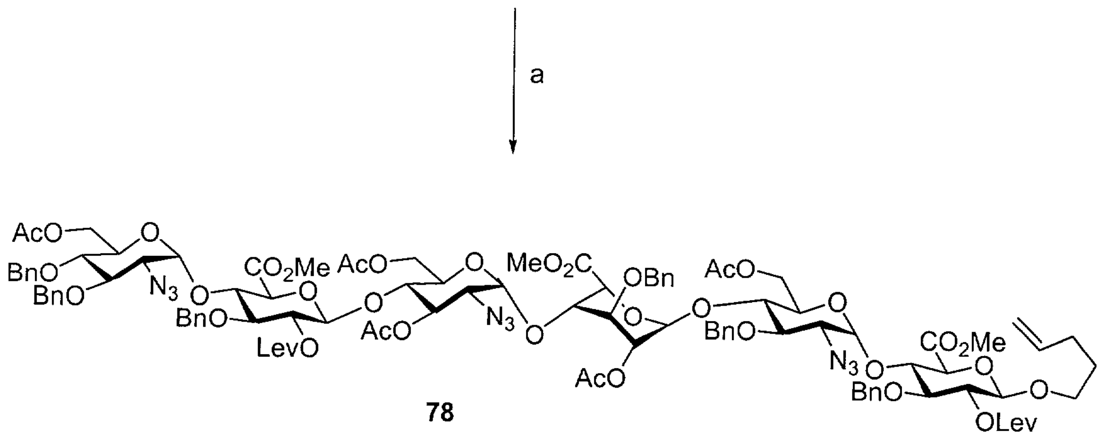
Figure 13



a) TMSOTf, CH_2Cl_2, -20°C, 93%; b) HF-pyridine, AcOH, THF, 82%; c) TMSOTf, CH_2Cl_2, -5°C, 63%; d) 1. TBAF, AcOH, THF; 2. Cl_3CCN, DBU, CH_2Cl_2, 0°C, 87% (2 steps).

Figure 14

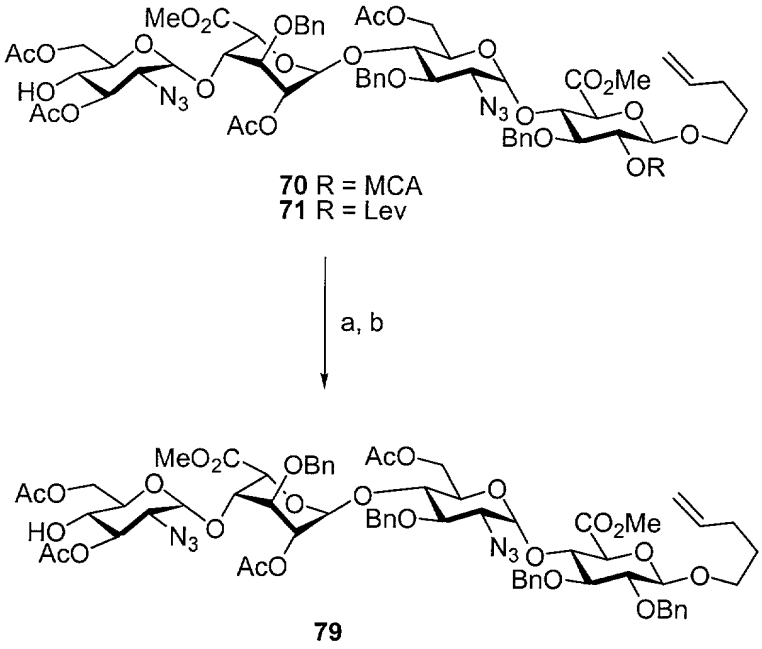
75 + 77



78

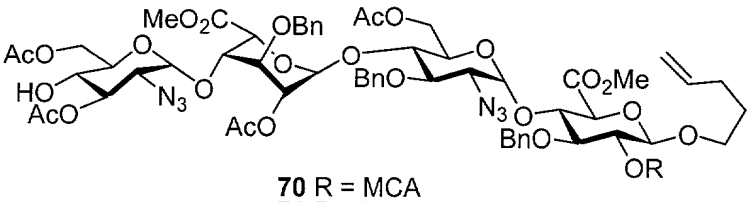
a) TMSOTf, CH_2Cl_2, -20°C, 62%;

Figure 15



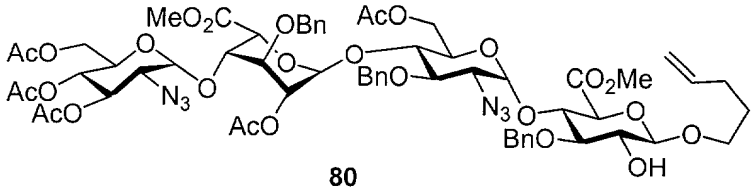
a) Thiourea, DMF, pyridine, rt, 24 h (90%) b) BnBr, Ag_2O, 4Å molecular sieves, CH_2Cl_2, rt, overnight (76%); c) Ac_2O, pyridine (quant.); d) NH_2NH_2-H_2O, pyridine, AcOH (90%); e) 1. aq. LiOH (0.7 M), H_2O_2 (50% aq.), THF overnight; 2. 4 M NaOH, rt overnight (82%); f) Et_3NSO_3, DMF, 50°C, overnight (50%); g) H_2, Pd/C, EtOH, water (quantitative); h) $PySO_3$, water (60%).

Figure 16



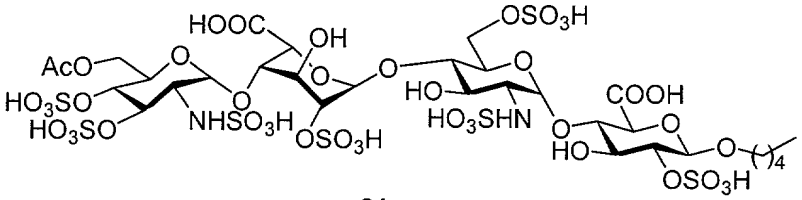
70 R = MCA
71 R = Lev

c,d



80

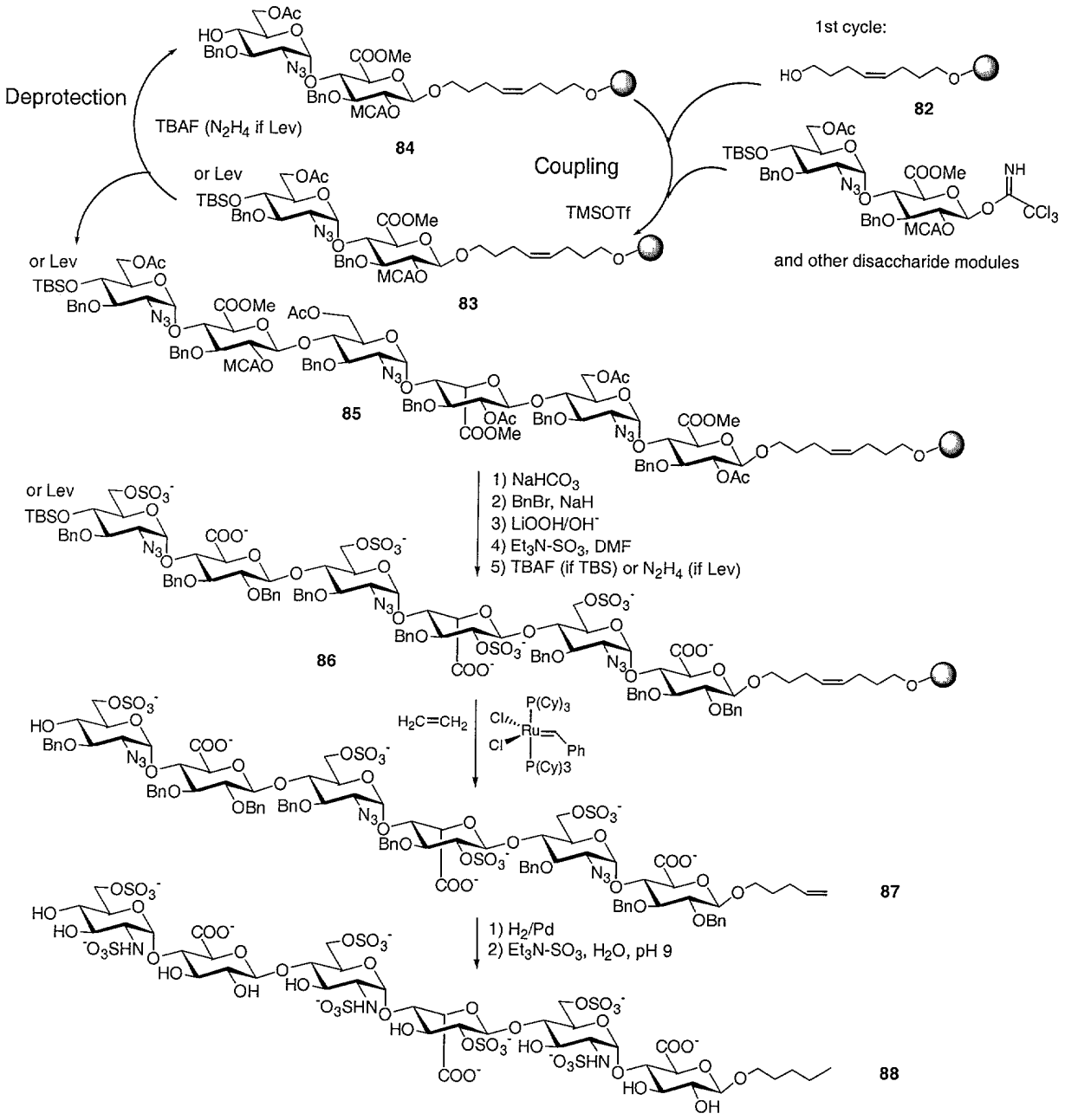
e, f, g, h



81

a) Thiourea, DMF, pyridine, rt, 24 h (90%) b) BnBr, Ag_2O, 4Å molecular sieves, CH_2Cl_2, rt, overnight (76%); c) Ac_2O, pyridine (quant.); d) NH_2NH_2-H_2O, pyridine, AcOH (90%); e) 1. aq. LiOH (0.7 M), H_2O_2 (50% aq.), THF overnight; 2. 4 M NaOH, rt overnight (82%); f) Et_3NSO_3, DMF, 50°C, overnight (50%); g) H_2, Pd/C, EtOH, water (quantitative); h) $PySO_3$, water (60%).

Figure 17


Deprotection
TBAF (N_2H_4 if Lev)
Coupling
TMSOTf
1st cycle:
and other disaccharide modules
1) $NaHCO_3$
2) BnBr, NaH
3) $LiOOH/OH^-$
4) Et_3N-SO_3, DMF
5) TBAF (if TBS) or N_2H_4 (if Lev)
$H_2C=CH_2$
1) H_2/Pd
2) Et_3N-SO_3, H_2O, pH 9